REMARKS

Claims

Claims 2, 8, 10–17 are pending of which claims 2, 8, 10 and 13–17 are currently under examination pursuant to the restriction requirement mailed September 27, 2007.

Claims 11–12 are withdrawn from consideration pursuant to the aforementioned restriction/election requirement.

Claims 1, 3–7 and 9 are cancelled without prejudice or disclaimer.

Claim amendments

Claims 13 and 17 are amended. It is submitted that the amendments do not raise new matter. Entry thereof is earnestly solicited.

Rejection under §112, ¶1

Claims 2, 8, 10 and 13–17 are rejected under this section as allegedly lacking written description of the antibody molecules and for allegedly failing to provide a disclosure of how to use such molecules in the claimed method(s).

Written Description

Reconsideration of this rejection in view of the USPTO's new written description guidelines (*Training Materials*, 1st Revision, March, 2008) is respectfully requested.

Applicants find that Example 13 of the *Training Materials* provides guidance on the written description of antibody molecules and manner of claiming them for satisfying the written description requirements under 35 USC §112, ¶1. Therein, an exemplary specification discloses that a protein designated antigen X has been isolated from HIV and is useful for detection of HIV infections. The specification describes purifying antigen X by gel filtration and discloses its amino acid sequence. The specification ***discusses*** antibodies which specifically bind to antigen X and ***asserts*** that these antibodies can be used in immunoassays to detect HIV (emphasis added). However, there is no working or detailed prophetic example of an antibody that binds to antigen X. Representative claim 1 is directed to a genus of antibody molecules which are capable of binding to antigen X (note, no functional activity, such as, for example, use thereof in immunoassays, is recited in the exemplary claim).

Claim 1. An isolated antibody capable of binding to antigen X.

The guidelines explicitly state that the exemplary specification satisfies the written description requirement with respect to the full scope of claim 1. The guidelines further explicitly state that "Considering the facts, including the routine art-recognized method of making antigen-specific antibodies, the adequate description of antigen X, the well-defined structural characteristics for the classes, subclasses and isotypes of antibody, the functional characteristics of antibody binding, and the fact that antibody technology was well developed and mature, one of skill in the art would have recognized that the disclosure of the adequately-described antigen X put the applicant in possession of antibodies which bind to antigen X."

In the present context, Applicants' claims are directed to treatment of cell proliferation, cell migration, invasivity or anti-apoptosis in the seven claimed cancers, wherein the cells of the cancer are characterized by increased G-protein mediated signal transduction, by administering an antibody against pro-HB-EGF. In view of the PTO's own written description guidelines, the specification's disclosure of a well-characterized antigen (such as, for example, pro-HB-EGF) provides more than adequate written description of the claimed antibody molecules. With respect to the manner of using such antibody molecules in immunotherapeutic applications, such was not only well-described in the medical literature but also routine for clinicians and medical professionals in the field of cancer biology. With respect to the features of cancer cells recited in the claims, for example, proliferation, migration, invasivity or anti-apoptotic behavior, the specification as-filed provides a detailed disclosure of various assays that can be used to determine such features. See, Figures 3-7 and the description thereof in the Examples section. Thus, these too are well-described. The same is true for GPCR-mediated signal transduction and the effect thereof on EGFR transactivation. See page 1, 2nd paragraph of the originally-filed application and the disclosure provided in WO 01/12182. As such, contrary to the PTO's contention, Applicants' specification provides more than an adequate written description of the various aspects of the claimed methods. Favorable reconsideration is respectfully requested.

Applicants respectfully disagree with the PTO's contention that "it is not predictable that the antibody [that binds to pro-HB-EGF protein] would also inhibit processing of said pro-HG-EGF." It is unclear how the PTO arrived at this contention. However, in order to facilitate prosecution, the claims have been amended to delete the functional language from the claims. The molecules are now described with respect to their ability to **bind to** pro-HB-EGF, and conform to the written description guidelines. Applicants' amendment of the claims is not to be construed as acquiescence to this or any other ground of rejection.

Withdrawal of the rejection is respectfully requested.

Enablement

Reconsideration of this rejection in view of the enclosed Ulrich declaration is respectfully requested. The experimental data enclosed herewith provides additional corroborating scientific evidence that the antibody molecules of the instant invention are useful in the treatment of treatment of cell proliferation, cell migration, invasivity or anti-apoptosis in colon cancer cells, kidney cancer cells, bladder cancer cells, prostate cancer cells, breast cancer cells, lung cancer cells or ovarian cancer cells, wherein the cancer cells are characterized by increased G-protein mediated signal transduction, as claimed. The results unequivocally demonstrate that the antibodies of the present invention inhibit EGFR phosphorylation in both control population of cancer cells (i.e., unstimulated cells) as well as cells that have been treated with GPCR agonists LPA and Thrombin. As is shown in Fig.1 of the enclosed declaration, kidney fibroblast tumor cells (COS-7 cells) treated with GPCR agonists LPA and Thrombin had increased tyrosine phosphorylation of EGFR (as measured via an ELISA assay). However, when the same EGFR transactivated cells were treated with anti-HB-EGF antibodies or the diphtheria toxin mutant CRM197, a complete reversal of EGFR transactivation was observed. For example, treatment with 20 µg/ml polyclonal anti-HB-EGF antibody completely inhibited LPA-induced activation of EGFR to basal levels. Similar results were obtained with respect to thrombin-induced EGFR transactivation and the inhibition thereof by the anti-pro-HB-EGF antibodies of the instant application. The results clearly show that antibodies of the present invention, such as polyclonal anti-HB-EGF antibodies, inhibit EGFR phosphorylation, and thus supports the fact that the specification as filed is enabling.

With regard to the effect of EGFR transactivation and its role in cancer etiology, a review of the originally-filed specification is respectfully requested. To this end, the specification expressly teaches to one of ordinary skill in the art that GPCR-induced EGFR transactivation leads to induction of various cellular processes, such as, for example, in increased cell proliferation, reduced FAS-induced apoptosis, increased cell migration, enhanced tumor cell invasion via the triple-membrane-passing signal (TMPS) pathway. GPCR agonists, such as LPA, elicit these changes *in vitro* in a variety of cells, including, lung, bladder, and kidney cancer cells (via increased tyrosine kinase phosphorylation). See, for example, the disclosure contained in Figures 3–7 and the summary provided in Table 1 of the originally-filed specification. Taken together, the data in the declaration and the Examples of the present application shows the

disclosed usefulness of antibody molecules of the instant invention in ameliorating cell proliferation, cell migration, invasivity or anti-apoptosis in the claimed cancers.

With respect to the usefulness of antibody molecules (i.e., immunotherapy) in the treatment of cancer, reconsideration of the rejection in view of Applicants' remarks in the reply filed December 11, 2008 and the evidentiary documents submitted therewith is respectfully requested. It should be further noted that the Courts have routinely held that "an applicant does not have to provide evidence sufficient to establish that an asserted utility **is true beyond a reasonable doubt**. *In re Irons*, 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965). Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the **asserted utility is more likely than not true** (emphasis added)." See MPEP §2164.07.

Withdrawal of the rejection is respectfully requested.

In view of the above remarks, favorable reconsideration is courteously requested. If there are any remaining issues which could be expedited by a telephone conference, the Examiner is courteously invited to telephone counsel at the number indicated below.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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Attorney Docket No.: WEICKM-0041

Date: September 3, 2009

Encl.
(a) Declaration